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Report

Neural Variability in Premotor Cortex Is Modulated by Trial History and Predicts Behavioral Performance

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SUMMARY

In the study of decision making, emphasis is placed on different forms of perceptual integration, while the influence of other factors, such as memory, is ignored. In addition, it is believed that the information underlying decision making is carried in the rate of the neuronal response, while its variability is considered unspecific. Here we studied the influence of recent experience on motor decision making by analyzing the activity of neurons in the dorsal premotor area of two monkeys performing a countermanding arm task. We observe that the across-trial variability of the neural response strongly correlates with trial history-dependent changes in reaction time. Using a theoretical model of decision making, we show that a trial history-monitoring signal can explain the observed behavioral and neural modulation. Our study reveals that, in the neural processes that culminate in motor plan maturation, the evidence provided by perception and memory is reflected in mean rate and variance respectively.

INTRODUCTION

Two-choice perceptual and motor tasks have been widely used to explore the neural mechanisms underlying decision-making processes (Logan and Cowan, 1984; Smith and Ratcliff, 2004; Gold and Shadlen, 2007; Verbruggen and Logan, 2008). Neural activity in parietal and frontal cortical areas has been shown to be correlated with behavioral performance of monkeys trained in specifically designed tasks (Platt and Glimcher, 1999; Gold and Shadlen, 2000, 2007; Cisek and Kalaska, 2005; Mirabella et al., 2011). In the last years, these binary simple tasks have been extended to account for multiple choices (Churchland et al., 2008; Albantakis and Deco, 2009). Although there has been progress in the understanding of the decision-making process in these tasks, little is known about how the recent history of the task influences the neural mechanisms underlying this process. In a previous theoretical investigation of the dynamics of working memory in optimal decision making, we have proposed that the integration of information from perception and memory requires temporal integration, supporting perception, and dynamic modulation of this temporal integration, serving memory (Verschure et al., 2003). A specific neural mechanism explaining such memory biasing, however, has not yet been described. One could argue that the across-trial variance of the neuronal response could reflect effects of task history. It has been proposed that variance of neuronal responses is correlated with the progress of motor preparation (Churchland et al., 2006) and that it is a general feature of cortical dynamics that is nonspecific with respect to the behavioral task at hand (Churchland et al., 2010). Here we investigate the possible signature of recent trial history in the variance of neuronal responses by analyzing the single-unit activity recorded in the dorsal premotor (PMd) area of two macaque monkeys performing a countermanding arm task (Mirabella et al., 2006).

The countermanding task has been extensively used to study motor decision mechanisms. It evaluates the ability to cancel a planned cued movement in response to the presentation of an infrequent Stop signal presented at variable delays (Stop signal delay, SSD; Figure 1A) from the time of presentation of the visual target (Logan and Cowan, 1984; Verbruggen and Logan, 2008). The overall behavioral performance in this task has been explained with the so-called race model (Logan and Cowan, 1984). The race model proposes that the behavioral outcome of the countermanding task is the result of a competition between a Go and a Stop process that evolves, driven by the accumulated sensory evidence, toward a decision threshold. Neuronal correlates of the movement generation process, as predicted by the race model, have been found in the modulation of firing rate (FR) of single-unit activity in the frontal eye field (FEF) and the superior colliculus (SC) for countermanding saccade tasks (Hanes and Schall, 1996; Paré and Hanes, 2003) and in the supplementary motor area (SMA) and PMd for countermanding arm tasks (Scangos and Stuphorn, 2010; Mirabella et al., 2011). However, all these results ignore the role of trial history in the task. After each trial in which a Stop cue is delivered (Stop trials), subjects increase their movement reaction time

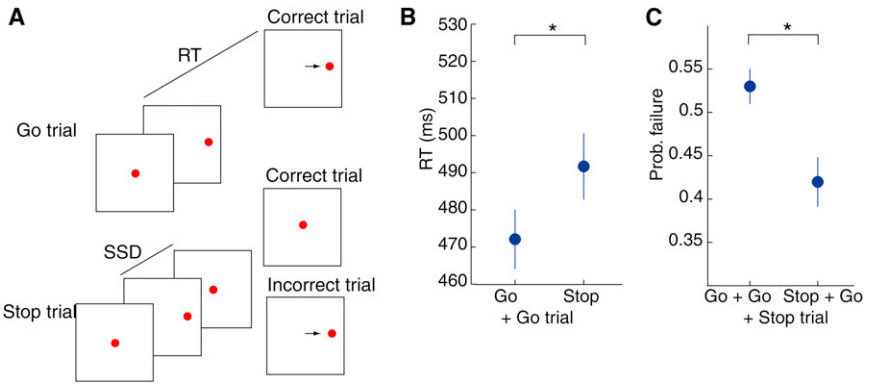

Figure 1. The Countermanding Task

(A) In a countermanding task, visual cues are presented either to induce movements (Go trial) or to prevent movements initiated by the Go signal (Stop trial). A central stimulus signals the start of the trial and the monkey is required to touch this cue with its hand. The start cue is followed (usually after 500–800 ms) by a visual cue (Go signal) that indicates the location to which a movement must be made. In the Go trials, the monkey has to execute a speeded reaching movement toward this peripheral target. During the Stop trials (33% of the trials), the central stimulus reappears after a variable delay, or Stop signal delay (SSD), instructing the monkey to withhold the planned movement, keeping the hand on the central stimulus. (B and C) Behavioral performance in a countermanding task relative to task history (53 experimental sessions). Error bars indicate SEM. (B) RT in Go trials when preceded by a Go or a Stop trial (Go + Go trial, 16,060 trials; Stop + Go trial, 6,671 trials; Kolmogorov-Smirnov test, *$p < 0.01$). (C) Probability of failure in a Stop trial when preceded by Go + Go trial or Stop + Go trial (Go + Go + Stop trial, 4,601 trials; Stop + Go + Stop trial, 2,116 trials; Kolmogorov-Smirnov test, *$p < 0.01$). See also Figure S1.

(RT), purportedly reflecting an increase in uncertainty about the current trial (Rieger and Gauggel, 1999; Mirabella et al., 2006; Emeric et al., 2007; Verbruggen and Logan, 2008; Nelson et al., 2010).

Here, using the data set reported in Mirabella et al. (2011), we investigate the behavioral adaptation and the modulation of the activity of reaching related neurons dependent on the temporal order of a trial in a sequence, i.e., the recent history of a trial. We observed that both behavior and variability of the neuronal responses were modulated by trial history. Using a computational model, we show that these effects can be explained in terms of a competitive process that is modulated by a monitoring signal.

RESULTS

To quantify the biasing of the neuronal response due to the history of a trial, we calculated the mean FR and the across-trial spike variability during Go trials that were sorted by different history conditions. We observed a significant and systematic difference in RT and neural response variability that held over a wide range of trial history conditions. These results suggested that, other than perceptual signals, neurons in PMd are also influenced by an additional input related to the history of the trial, i.e., memory. To validate this hypothesis, we studied the response of a mean-field approximation of a spiking neural model (Wilson and Cowan, 1972) in a simulated countermanding task. We observed that an additional monitoring-related signal can directly account for the observed changes in the neural response variability and the behavioral performance.

Behavioral Responses

We analyzed the behavioral responses of the monkeys looking at their RT in Go trials and probability of failure to cancel a planned movement in Stop trials. Consistent with previous work (Emeric et al., 2007; Pouget et al., 2011), we observed that the mean RT of the monkeys increases when the current Go trial was preceded by a Stop trial (Figure 1B), in contrast to when it was preceded by a Go trial. This confirms that performance is modulated by trial history. In addition, the SD of the RT was higher when a Go trial was preceded by a Stop trial than when preceded by a Go trial (see Figure S1 available online). Moreover, a longer RT was associated with a lower probability of failure in the following trial (Figure 1C), i.e., successful cancellation was more likely in a Stop (t) trial that followed a sequence of Go ($t - 1$) and Stop ($t - 2$) as opposed to a sequence comprising two Go trials.

Neural Correlate of the Decision Process

To assess the neural correlate of the decision process, we analyzed the modulation of the mean FR of the neurons and their across-trial spike variability, as measured by the variance of conditional expectation (VarCE) (Churchland et al., 2011) during motor preparation. For this analysis we used only Go trials from the time of the presentation of the Go signal until arm movement onset. We sorted the data with respect to the type of trial that was preceding the current Go trial: a Go or a Stop trial. We observed that after the presentation of the Go signal, both the FR and the VarCE increased until they reached a peak value at about 150 ms before movement onset (Figures 2A and 2B). After this peak, the mean FR and the VarCE gradually decreased to their baseline (right panels of Figures 2A and 2B). The mean FR in the analysis epoch did not significantly differ between the two conditions, i.e., whether the current Go trial was preceded by a Stop or a Go trial. In contrast, VarCE displayed a strong modulation by the task history and was significantly higher in case the preceding trial was a Stop as opposed to a Go trial (Figure 2B). Single-unit analyses showed a consistent effect across the whole population (Figure S2A). We also tested the correlation of task history with VarCE during Stop trials in two different contexts: when a Stop trial was preceded by Go ($t - 1$) and Stop ($t - 2$) trials or by two consecutive Go trials. We observed the same modulation in VarCE by task history (Figure S2B). Interestingly, the difference in VarCE between both conditions disappeared about 70 ms after the presentation of the Stop signal. This latency is consistent with the average processing delay of visual information in PMd (Cisek and Kalaska, 2005).

In a next analysis, we assessed the relationship between task history, VarCE, and performance (Figures 2C, 2D, and S2C). This

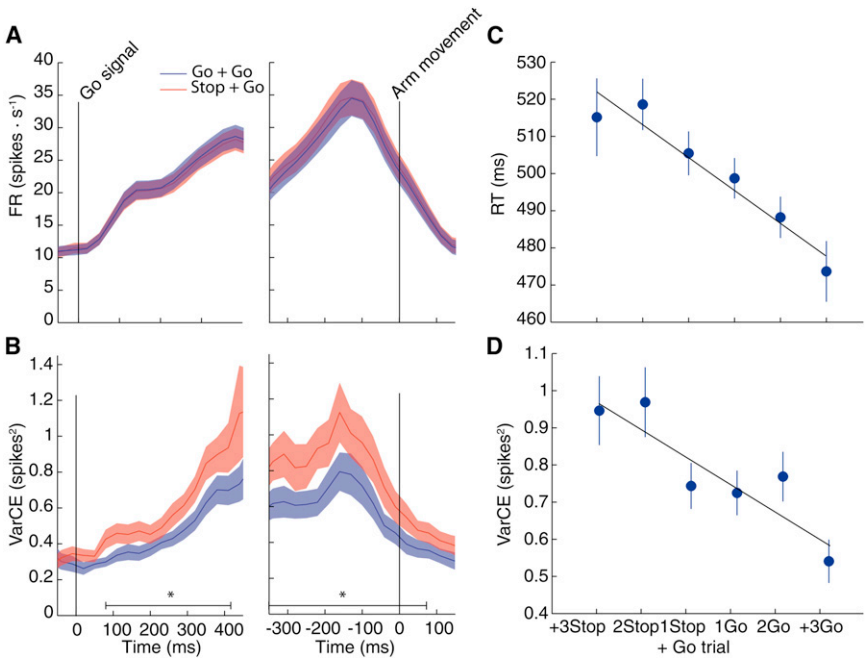

Figure 2. Neuronal Dynamics during the Countermanding Task

(A and B) Neural activity is aligned to Go signal (left) and arm movement (right) onsets. Shaded areas indicate SEM. (A) Mean FRs in Go trials when preceded by a Stop (red) or Go (blue) trial (Kolmogorov-Smirnov test, $p > 0.05$). Results are obtained from 142 neurons (Go + Go trial, 16,060 trials; Stop + Go trial, 6,671 trials). (B) VarCE for the same two conditions as in (A). VarCE is significantly different from 80 to 410 ms after the onset of the Go signal (Kolmogorov-Smirnov test, *$p < 0.01$) and from −350 to 70 ms when aligned to movement onset (Kolmogorov-Smirnov test, *$p < 0.01$). (C and D) RT (C) and VarCE (D) during a Go trial in six different trial history conditions when it was preceded by three or more (+3) Stop trials (850 trials), two Stop trials (1,353 trials), one Stop trial (4,468 trials), one Go trial (4,578 trials), two Go trials (3,257 trials), and three or more (+3) Go trials (8,225 trials). Error bars indicate SEM. Data are obtained from same 142 neurons. See also Figure S2.

analysis revealed that mean and SD of RT closely mirrors the effect of task history on VarCE over a wide range of task history conditions. The three factors, mean RT, SD of RT, and VarCE, increased with an increase in the number of previous Stop trials, while they decreased with an increase in the number of preceding Go trials. Moreover, changes in mean RT over a range of trial history conditions are due to systematic shifts of the entire RT distributions (Figure S2D). We observe that the mean RTs are very well correlated with VarCE (Figure 3A) and that RT and VarCE distributions seem to have similar shape (Figure 3B). The mean FR for the same conditions did not show any variation (Figure S2E). Interestingly, the modulation of VarCE also depends on the difficulty of the previous trial (Figure S2F), so that its value increased as the SSD in the Stop trial preceding the Go trial increased. Thus, these results suggest that the influence of task history is reflected in the variance of neuronal activity in PMd and that both variables, VarCE and trial history, are linearly correlated with performance.

Mean-Field Approximation

In order to understand the neural mechanisms causing the observed behavioral and across-trial neuronal response variability differences due to varying trial history conditions, we used a mean-field approximation (Wilson and Cowan, 1972) of a biophysically based binary decision-making model (Figure 4A). The model receives two segregated inputs: perceptual evidence provided by the visual cues (Stop and Go signals) and a task history signal provided by a monitoring system. The model has two populations of excitatory neurons: one population is sensitive to the appearance of the Go signal (λ_{go}; Go pool), while the other population is sensitive to the appearance of the Stop signal (λ_{stop}; Stop pool). The two populations mutually inhibit each other. In the absence of any of the two visual signals, both λ_{go} and λ_{stop} are equal to 0. A monitoring process modulates the strength of the input (λ) to each group of neurons simulating different trial history conditions: λ increases its value as the number of Stop trials preceding a Go trial increases and decreases its value as the number of Go trials preceding a Go trial increases (Figure 4B). We observe that the model reproduces the same relationship between the probability of failure and SSDs as observed during the countermanding task, i.e., the probability of failing in the Stop trials increases as the SSD increases (Mirabella et al., 2006) (Figure S3A).

To compute decision times in the simulations, we considered that the decision process was terminated when the difference in activity between Go and Stop pools was above a fixed threshold (Roxin and Ledberg, 2008). The RT was calculated by adding 150 ms to the decision time, consistent with the peak in FR observed 150 ms before movement onset in the physiological data (Figure 2A). The mean and SD of RT obtained from the simulations (Figures 4C and S3B) exhibit the same trend as observed in the physiology of PMd (Figures 2C and S2C): the mean and SD of RT in a Go trial are longer/shorter as the number of preceding Stop/Go trials increase.

Consistent with our analysis of the physiological data, the different simulated trial history conditions have a similar impact on the variability of the Go pool response (Figure 4D). This impact of the monitoring signal λ on RT and VarCE can be intuitively understood in terms of the competition between the two neuronal pools Stop and Go through mutual inhibition (Figure 4A). The model is tuned such that the firing rate of the Go pool is not affected by this neuronal competition (Figure S3C), as observed in the response of the neurons we have analyzed (Figure S2E). We observe that, given these assumptions that reflect the physiological properties of PMd, the addition of the monitoring signal leads to the modulation of the effect that the Stop pool has on the dynamics of the overall network, leading to a change in the mean RT. In addition, when the influence of the Stop pool on the

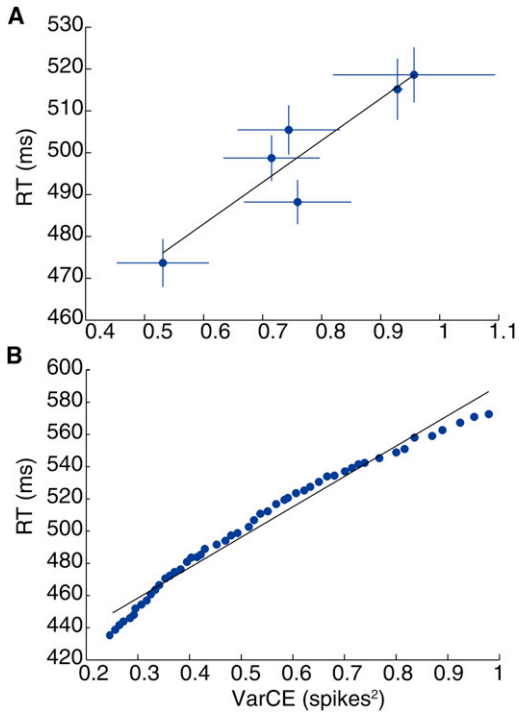

Figure 3. The Relationship between Performance and VarCE

(A) Mean RT is fitted by VarCE using a linear regression ($R = 0.93$ and $p < 0.01$). Data points are as in Figures 2C and 2D. Error bars indicate SEM. (B) Quantile-Quantile plot of the interquartile range of RT and VarCE distributions formed by pooled data from all conditions. The data points are linearly correlated ($R = 0.99$ and $p < 0.01$), suggesting a high similarity in the shape of the distributions.

dynamics is increased, the intrinsic noise of the system starts to have a larger impact on the performance and dynamics of the network, resulting in an increase in VarCE and RT variability. Indeed, it has been demonstrated that the neural response variability changes with the strength of the input to this model, due to a shift in the distance from the working point of the system to the bifurcation point (Deco and Hugues, 2012; Roxin and Ledberg, 2008). Here we exploit this effect through the monitoring signal. Hence, perceptual input defines the mean rate, while the history-dependent monitoring signal defines a modulation around this rate expressed in VarCE. These results confirm that the response variability we observed in PMd can be seen as a signature of trial history and predict the existence of a system that both monitors the recent history of a task and modulates competition between pools of neurons dedicated to Go and Stop.

DISCUSSION

We have investigated the hypothesis that perceptual cues and memory of trial history are integrated in the decision-making process underlying the countermanding task. Our analyses of the responses of neurons in PMd of monkeys performing a countermanding arm task show the influence of recent trial history on both the performance of monkeys and on the variability of neuronal responses in PMd. We show that the behavior of the monkeys becomes increasingly more conservative (longer RT) when a Go trial was recently preceded by one or more Stop trials and increasingly hastier (shorter RT) when it was recently preceded by one or more Go trials, as previously reported (Rieger and Gauggel, 1999; Emeric et al., 2007; Verbruggen and Logan, 2008; Nelson et al., 2010; Mirabella et al., 2006). We show that the behavioral performance is linearly correlated with changes in the variability of the neural response. To validate the possible signature of trial history in neural response variability, we performed an additional theoretical study using a mean-field approximation of a spiking neural model. We show that changes in the strength of a modulatory input that reflects trial history accounts for the observed changes in behavior and neural response variability, suggesting the existence of a trial history-monitoring system in the brain. Our study provides a neural correlate for task history and its impact on the neuronal substrate of decision making and is a further example of how adaptive behavior is monitored and orchestrated in the brain (Walton et al., 2004; Ito et al., 2003).

One of the weaknesses of using VarCE as a measurement of the across-trial variability lies in the estimation of the scaling factor ϕ. We computed it separately for each neuron (see Experimental Procedures), and the obtained distribution of the values of ϕ was consistent with the ones previously reported for the neocortex (Figure S2G) (Shadlen and Newsome, 1998; Nawrot et al., 2008). To check the robustness of our results to variations in the value of ϕ, we repeated our analyses (Figure 2B) but setting the same value of ϕ for each neuron. We observed that the difference in VarCE between history conditions is independent on the value of ϕ used (Figure S2H).

Similar to VarCE, the Fano Factor (spike count variance divided by spike count mean) has been used to calculate the across-trial variability of neural responses. Although in most cases both measurements are considered to be equivalent, for significant changes in mean FR, the VarCE has shown to be more robust than the Fano Factor (Churchland et al., 2011). However, our conclusions hold for both the Fano Factor and the VarCE (see Figures S2I and S2J) and are further supported by the equivalent histogram obtained from the interspike interval observed in a Go trial preceded by different sequences of trials, i.e., with different history (see Figure S2K). Hence, our results are robust with respect to the specific method used to obtain a measure of variability.

Our results suggest that the observed change in strategy during the task might be due to an increase or decrease in the uncertainty about Stop cue appearance in the current trial, suggesting a relationship between trial history and uncertainty. Under this interpretation, one might speculate that the degree of the monkeys' uncertainty is updated based on the trial history and increases as a function of the number of Stop trials. Subsequently, this relationship implies a direct link between uncertainty and variability: higher uncertainty is related to a higher variability in the neural response and a longer and more variable RT. Our simulation predicts the existence of a system that monitors either trial history itself or uncertainty based on trial history and updates its value according to new incoming information, i.e., actions and their outcome in a new trial. This definition of uncertainty is consistent with previous work in which uncertainty is defined in terms of the accuracy to predict the possible

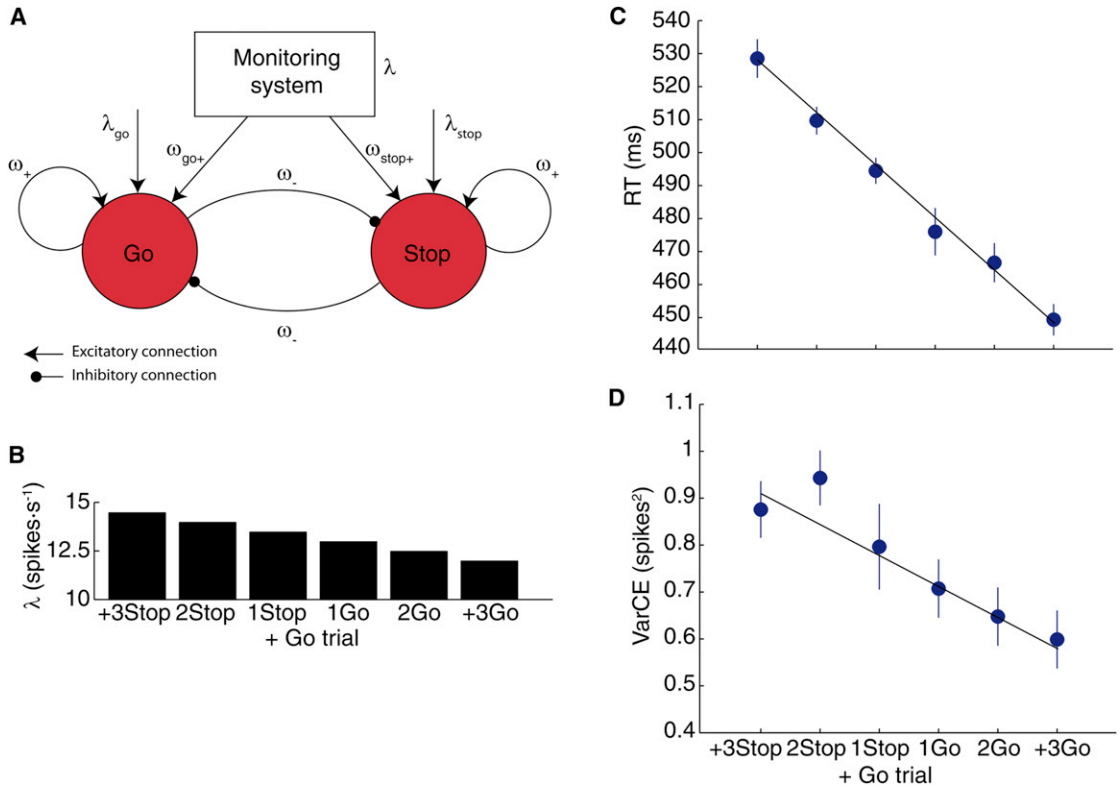

Figure 4. Mean-Field Approach

(A) Network structure of the binary decision model. The "Go" pool is selective for the Go signal (λ_{go}), while the "Stop" pool is selective for the Stop signal (λ_{stop}). The two pools mutually inhibit each other (ω_-) via inhibitory pools (not represented) and have self-excitatory recurrent connections (ω_+). The "Monitoring system" is connected with the two selective pools. The synapses that connect the "Monitoring system" with the "Go" and "Stop" pools have different strength ω_{go+} and ω_{stop+}. (B) Firing rate value of the signal provided by the monitoring system. The value of this signal depends on the history of the current trial. The value of λ increases as the number of Stop trials preceding a Go trial increases and decreases as the number of Go trials preceding a Go trial increases. (C and D) RT (C) and VarCE (D) of the response of the "Go" pool sorted by the recent history of a trial. Simulation results were obtained from 10,000 trials grouped in ten sessions of 1,000 trials each. Error bars indicate SEM. See also Figure S3.

consequences of actions (Huettel et al., 2005; Yoshida and Ishii 2006). For instance, in the countermanding task, after a Stop trial both humans and monkeys increase their expectation about the probability of a next trial including a Stop signal (Emeric et al., 2007).

The use of a mean-field approximation of a realistic network of integrate-and-fire neurons (see Experimental Procedures and Supplemental Experimental Procedures) allows us to study the dynamics of the decision-making process from the perspective of the neuronal substrate. We have shown that the biasing of the neural responses and the consequent changes in the behavioral strategy during different trial history conditions could be caused by a signal coming from a system that monitors the recent history of a trial and that directly changes the strength of the competition between the neural populations involved in the decision making. This modulation in the competition influences the variability of the across-trial average activity, while the average response of the population correlated with the execution of movement (Go pool) is the same due to the balance in the excitatory and inhibitory connections of the network. Changes in the behavioral strategy could be explained with the same mechanism, i.e., due to a modulation in the strength of the competition between neuronal populations, a suprathreshold difference in their activity will take varying amounts of time to be generated. Hence, according to our proposal, VarCE is a derived measure caused by a difference in the strength of the competitive process with different trial history conditions. Because our neural data are based on single-unit recordings, it is difficult to conceive how VarCE could be read out. However, areas like primary motor cortex, posterior parietal cortex, SMA, and cingulate cortex (Johnson et al., 1996; Johnson and Ferraina, 1996) that read information from PMd would have access to the population and, in this case, an instantaneous measure of variability could be possible by trading off temporal integration for spatial integration. This would raise the question of whether this redundant representation of trial history would be necessary. The answer to this question is, however, out of the scope of this study.

Changes in the initiation of activity accumulation in FEF and SC have shown to be correlated with task history-dependent changes in performance (Pouget et al., 2011). We did not observe, at the population level, any modulation of firing rate in

PMd after adaptive response time adjustment. A possible explanation is that the functional organization of the neural network controlling eye movements is very different of that controlling limb movements (see also Discussion in Mirabella et al., 2011). We exclude that the modulation of FEF could be a source of the neural response variability we observed. In fact, our recording region included the more rostral portion of PMd but not supplementary eye fields (Mirabella et al., 2011). Only this last portion receives input from FEF, while the rostral PMd is preferentially connected with dorsolateral prefrontal regions (Luppino et al., 2003). A monitoring signal could be provided by the connection of PMd with cingulate cortex (Johnson and Ferraina, 1996; Luppino et al., 2003). The anterior portion of cingulate cortex has been shown, in humans, to display trial history modulation of baseline activity (Domenech and Dreher, 2010). Further studies are needed to clarify all these aspects in detail.

Our study shows a key role of the across-trial variability of the firing rates as a signature of trial history during decision making, confirming an earlier theoretical prediction (Verschure et al., 2003) and adding an extra variable to be considered in future experimental and theoretical studies. In the context of the countermanding arm task, the information provided by perception and memory to the decision-making process is reflected in different aspects of the neuronal activity: mean FR and across-trial variance respectively. We have shown that the latter is linearly related to the RT and the trial history experienced by the monkeys. Our results imply that there is a continuous monitoring of trial history that, combined with the current perceptual evidence, is used to make a decision. An important question is now whether the origin of this monitoring process is internal (Domenech and Dreher, 2010) or external (Zandbelt and Vink, 2010) to the PMd and its immediate cortical efferent and afferent areas.

EXPERIMENTAL PROCEDURES

Behavior and Physiology

Two adult male rhesus macaques (Macaca mulatta; monkey S and monkey L) weighing 7–8 kg were used. Details of the experimental procedures have been provided in Mirabella et al. (2011). Monkeys were trained to perform a countermanding reaching task. It consists of a random mix of 67% Go trials and 33% Stop trials. All trials began with the appearance of a stimulus at the center of a touch screen (Figure 1A). Monkeys were required to touch the stimulus with their fingers, within 2 s, and hold it for a variable period of 500–800 ms. Thereafter, in the Go trials, the central stimulus disappeared and, simultaneously, a target appeared (Go signal) randomly at one of two possible opposite peripheral positions. To get a juice reward, monkeys had to reach the target within a maximum time, named upper reaction time (to discourage monkeys from adopting the strategy of excessively slowing down the RTs), and to maintain their fingers on it for 300 ms. Stop trials differed from the Go trials because at a variable delay (SSD) after the Go signal was presented, the central stimulus reappeared (Stop signal). In these instances, to earn the juice, the monkeys had to inhibit the pending movements, holding the central target for 300 ms. Monkeys were given an auditory feedback when their responses in either Go or Stop trials were correct. A countermanding session consisted of 480 trials. In the Stop trials, the successful inhibition of the planned movement critically depends on the duration of SSD. Cancelling the movements becomes increasingly more difficult as the SSD is larger. In the two monkeys, we used different values of SSDs (see Mirabella et al., 2011 for details) with the goal to obtain a good performance, i.e., an average probability of successful suppression of the movement close to 0.5.

Data Analysis

Behavioral Performance

Probability of failure and RT distributions were calculated from the mean values obtained for each experimental session. The SD of RT distribution was obtained from the SD of RT for each experimental session.

Estimation of Mean Firing Rate

Starting from the original data set (Mirabella et al., 2011), we selected 142 neurons obtained from 53 experimental sessions in the two monkeys. Neurons selected are those with reaching-related modulation, i.e., their average FR in the RT was significantly higher (Tukey Kramer test, $p < 0.05$) than the activity measured 400 ms before target appearance. We computed mean FR responses (Figure 2A) using windows of 60 ms over trials with same recent history. All references to time correspond to the midpoint of the window. Varying the size of the window did not result in significant changes (data not shown). The significance test (Kolmogorov-Smirnov test) was computed using a 60 ms nonoverlapping window.

Estimation of Neural Variability

To calculate the across-trial variability of the neural response, we follow the method in Churchland et al. (2011) in which the total calculated variance is approximated as the sum of the VarCE and the point process variance (PPV). VarCE is then estimated ($s^2_{\langle N_i \rangle}$) by subtracting an estimated value of PPV from the total calculated variance:

$$s^2_{\langle N_i \rangle} = Var[N_i] - \phi \overline{N}_i$$

where N_i and $\overline{N}_i$ are spike counts and the mean spike counts in epoch i for one neuron and trial history condition and ϕ is a scaled factor that corresponds to the minimum value of the calculated Fano Factor for each neuron (see Churchland et al., 2011 and Supplemental Experimental Procedures for details). To compute VarCE, we used the same time window as in the estimation of the mean.

To calculate VarCE in the six history conditions shown in Figure 2D, we averaged the value of VarCE in the interval between 80 ms and 410 ms after the Go signal onset. We used this range because it is the time interval in which VarCE in a Go trial is significantly different when preceded by a Go trial than when preceded by a Stop trial (Figure 2B). The significance test (Kolmogorov-Smirnov test) was computed using a 60 ms nonoverlapping window.

Model and Simulations

We used a standard neuronal model proposed by Wilson and Cowan (1972). It is a mean-field approximation of a realistic complex network of spiking integrate-and-fire neurons. The dynamics of the network can be described through two differential equations each of them referring to each population (pool) of neurons (in our case "Go" and "Stop" pools):

$$\tau \frac{dU_{go}(t)}{dt} = -U_{go}(t) + f\left(\omega_{go+}\lambda + \lambda_{go} + \omega_{+}U_{go} - \omega_{-}U_{stop}\right) + \sigma\xi(t)$$

$$\tau \frac{dU_{stop}(t)}{dt} = -U_{stop}(t) + f\left(\omega_{stop+}\lambda + \lambda_{stop} + \omega_{+}U_{stop} - \omega_{-}U_{go}\right) + \sigma\xi(t)$$

where U stands for the average firing rate of a pool, ω stands for the different weight of the connections, λ defines external inputs to the network, and the function $f(.)$ is a sigmoidal function defined as:

$$f(x) = \frac{F_{max}}{1 + e^{\frac{-(x-\theta)}{k}}}$$

where F_{max} denotes the firing rate value to which the population of neurons will saturate independently of the strength of the external input signal. In this study, we have used the values of: $\tau = 20$ ms, $\omega_{go+} = 0.70$, $\omega_{stop+} = 1$, $\omega_{+} = 1$, $\omega_{-} = 1.5$, $F_{max} = 40$ spikes × s^{-1}, $k = 22$ spikes × s^{-1}, $\theta = 15$ spikes × s^{-1}, and $\lambda_{go} = 7.3$ spikes × s^{-1} when the appearance of the Go signal is simulated, $\lambda_{stop} = 0$, and λ linearly varies its value from condition to condition following the trend in Figure 4B. It can be described by the equation: $\lambda = -0.35x + 18$, where x goes from 1 to 6 to describe the trial history conditions: +3Stop, 2Stop, 1Stop, 1Go, 2Go, and +3Go. The decision was considered to end when the difference between Go and Stop pools response was above 15 spikes × s^{-1}.

The fluctuations of the network are modeled by the term ξ, which adds an additive Gaussian noise (with mean 0 and variance 1) to the average firing rate. This noise represents the effects of a finite number of neurons in the network. The term $\sigma = 2$ spikes $\times$ s^{-1} in our simulations.

VarCE of the simulated response of the network was calculated by estimating the spike counts from the mean firing rate of the Go pool. The spike counts were estimated by using a scale factor of 12, which depends on the population size, following a standard procedure (Albantakis and Deco, 2009; Wang, 2002). We did this scaling in order to fit quantitatively the experimental data.

SUPPLEMENTAL INFORMATION

Supplemental Information includes three figures and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2013.02.006.

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REFERENCES

Albantakis, L., and Deco, G. (2009). The encoding of alternatives in multiple-choice decision making. Proc. Natl. Acad. Sci. USA *106*, 10308–10313.

Churchland, M.M., Yu, B.M., Ryu, S.I., Santhanam, G., and Shenoy, K.V. (2006). Neural variability in premotor cortex provides a signature of motor preparation. J. Neurosci. *26*, 3697–3712.

Churchland, A.K., Kiani, R., and Shadlen, M.N. (2008). Decision-making with multiple alternatives. Nat. Neurosci. *11*, 693–702.

Churchland, M.M., Yu, B.M., Cunningham, J.P., Sugrue, L.P., Cohen, M.R., Corrado, G.S., Newsome, W.T., Clark, A.M., Hosseini, P., Scott, B.B., et al. (2010). Stimulus onset quenches neural variability: a widespread cortical phenomenon. Nat. Neurosci. *13*, 369–378.

Churchland, A.K., Kiani, R., Chaudhuri, R., Wang, X.-J., Pouget, A., and Shadlen, M.N. (2011). Variance as a signature of neural computations during decision making. Neuron *69*, 818–831.

Cisek, P., and Kalaska, J.F. (2005). Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. Neuron *45*, 801–814.

Deco, G., and Hugues, E. (2012). Neural network mechanisms underlying stimulus driven variability reduction. PLoS Comput. Biol. *8*, e1002395.

Domenech, P., and Dreher, J.C. (2010). Decision threshold modulation in the human brain. J. Neurosci. *30*, 14305–14317.

Emeric, E.E., Brown, J.W., Boucher, L., Carpenter, R.H., Hanes, D.P., Harris, R., Logan, G.D., Mashru, R.N., Paré, M., Pouget, P., et al. (2007). Influence of history on saccade countermanding performance in humans and macaque monkeys. Vision Res. *47*, 35–49.

Gold, J.I., and Shadlen, M.N. (2000). Representation of a perceptual decision in developing oculomotor commands. Nature *404*, 390–394.

Gold, J.I., and Shadlen, M.N. (2007). The neural basis of decision making. Annu. Rev. Neurosci. *30*, 535–574.

Hanes, D.P., and Schall, J.D. (1996). Neural control of voluntary movement initiation. Science *274*, 427–430.

Huettel, S.A., Song, A.W., and McCarthy, G. (2005). Decisions under uncertainty: probabilistic context influences activation of prefrontal and parietal cortices. J. Neurosci. *25*, 3304–3311.

Ito, S., Stuphorn, V., Brown, J.W., and Schall, J.D. (2003). Performance monitoring by the anterior cingulate cortex during saccade countermanding. Science *302*, 120–122.

Johnson, P.B., and Ferraina, S. (1996). Cortical networks for visual reaching: intrinsic frontal lobe connectivity. Eur. J. Neurosci. *8*, 1358–1362.

Johnson, P.B., Ferraina, S., Bianchi, L., and Caminiti, R. (1996). Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. Cereb. Cortex *6*, 102–119.

Logan, G.D., and Cowan, W.B. (1984). On the ability to inhibit thought and action: a theory of an act of control. Psychol. Rev. *91*, 295–327.

Luppino, G., Rozzi, S., Calzavara, R., and Matelli, M. (2003). Prefrontal and agranular cingulate projections to the dorsal premotor areas F2 and F7 in the macaque monkey. Eur. J. Neurosci. *17*, 559–578.

Mirabella, G., Pani, P., Paré, M., and Ferraina, S. (2006). Inhibitory control of reaching movements in humans. Exp. Brain Res. *174*, 240–255.

Mirabella, G., Pani, P., and Ferraina, S. (2011). Neural correlates of cognitive control of reaching movements in the dorsal premotor cortex of rhesus monkeys. J. Neurophysiol. *106*, 1454–1466.

Nawrot, M.P., Boucsein, C., Rodriguez Molina, V., Riehle, A., Aertsen, A., and Rotter, S. (2008). Measurement of variability dynamics in cortical spike trains. J. Neurosci. Methods *169*, 374–390.

Nelson, M.J., Boucher, L., Logan, G.D., Palmeri, T.J., and Schall, J.D. (2010). Nonindependent and nonstationary response times in stopping and stepping saccade tasks. Atten. Percept. Psychophys. *72*, 1913–1929.

Paré, M., and Hanes, D.P. (2003). Controlled movement processing: superior colliculus activity associated with countermanded saccades. J. Neurosci. *23*, 6480–6489.

Platt, M.L., and Glimcher, P.W. (1999). Neural correlates of decision variables in parietal cortex. Nature *400*, 233–238.

Pouget, P., Logan, G.D., Palmeri, T.J., Boucher, L., Paré, M., and Schall, J.D. (2011). Neural basis of adaptive response time adjustment during saccade countermanding. J. Neurosci. *31*, 12604–12612.

Rieger, M., and Gauggel, S. (1999). Inhibitory after-effects in the stop signal paradigm. Br. J. Psychol. *90*, 509–518.

Roxin, A., and Ledberg, A. (2008). Neurobiological models of two-choice decision making can be reduced to a one-dimensional nonlinear diffusion equation. PLoS Comput. Biol. *4*, e1000046.

Scangos, K.W., and Stuphorn, V. (2010). Medial frontal cortex motivates but does not control movement initiation in the countermanding task. J. Neurosci. *30*, 1968–1982.

Shadlen, M.N., and Newsome, W.T. (1998). The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. J. Neurosci. *18*, 3870–3896.

Smith, P.L., and Ratcliff, R. (2004). Psychology and neurobiology of simple decisions. Trends Neurosci. *27*, 161–168.

Verbruggen, F., and Logan, G.D. (2008). Response inhibition in the stop-signal paradigm. Trends Cogn. Sci. *12*, 418–424.

Verschure, P.F.M.J., Voegtlin, T., and Douglas, R.J. (2003). Environmentally mediated synergy between perception and behaviour in mobile robots. Nature *425*, 620–624.

Walton, M.E., Devlin, J.T., and Rushworth, M.F.S. (2004). Interactions between decision making and performance monitoring within prefrontal cortex. Nat. Neurosci. *7*, 1259–1265.

Wang, X.-J. (2002). Probabilistic decision making by slow reverberation in cortical circuits. Neuron *36*, 955–968.

Wilson, H.R., and Cowan, J.D. (1972). Excitatory and inhibitory interactions in localized populations of model neurons. Biophys. J. *12*, 1–24.

Yoshida, W., and Ishii, S. (2006). Resolution of uncertainty in prefrontal cortex. Neuron *50*, 781–789.

Zandbelt, B.B., and Vink, M. (2010). On the role of the striatum in response inhibition. PLoS ONE *5*, e13848.